# Right on track: Towards improving DBS patient selection and care

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# CHAPTER 4

## Intraoperative test stimulation of the subthalamic nucleus aids postoperative programming of chronic stimulation settings in Parkinson's disease

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# Abstract

**Background**

It is unknown whether intraoperative testing during awake Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) can be used to postoperatively identify the best settings for chronic stimulation.

**Objective**

To determine whether intraoperative test stimulation is indicative of postoperative stimulation results.

**Methods**

Records of consecutive Parkinson's Disease patients who received STN DBS between September 2012 and December 2017 were retrospectively analyzed. The best depth identified after intraoperative stimulation via the microelectrode's stimulation tip was compared with the depth of the contact selected for chronic stimulation after a standard monopolar contact review. Moreover, thresholds for induction of clinical effects (optimal improvement of rigidity and induction of side-effects) were compared between stimulation at the postoperatively selected contact and at the corresponding intraoperative depth.

**Results**

Records of 119 patients were analyzed (mean (SD) age 60.5 (6.5) years, 31.9% female, 238 STNs). In 75% of cases, the postoperatively selected contact corresponded with the intraoperative depth with the largest therapeutic window or was immediately dorsal to it. Higher stimulation intensities were required postoperatively than intraoperatively to relieve rigidity ($p=0.002$) and induce capsular side-effects ($p=0.016$).

**Conclusion**

In the majority of cases, the postoperative contact for chronic stimulation was at a similar level or immediately dorsal with respect to the identified best intraoperative depth. Postoperatively, relief of rigidity and induction of capsular side-effects occur at higher stimulation intensities than during intraoperative test stimulation.

# Introduction

Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) is an effective treatment to improve Parkinson's Disease (PD) symptoms and quality of life.[1-3] Optimal placement of DBS leads is required to induce maximal motor improvement at low stimulation intensities, with high thresholds for stimulation-induced side-effects.[4] During surgery, simultaneous microelectrode recording (MER) tracks may optimize target localization by identifying typical STN electrical activity.[5-6] Moreover, test stimulation with the microelectrode tip can help identifying the best location for the definitive lead by assessing both motor improvements and stimulation-induced side-effects.[7]

During the early postoperative period, a monopolar contact review is generally performed to identify the best contact for chronic stimulation.[8] This time-consuming procedure is in our experience often poorly tolerated by patients.



It is unknown if the results of intraoperative testing are indicative of postoperative stimulation settings. The aim of this study was to investigate how the results of intraoperative testing compare to results of the postoperative contact review. This knowledge could ultimately make postoperative testing more efficient and less burdensome to patients.

# Methods

All consecutive PD patients who received STN DBS at the Haga Teaching Hospital / Leiden University Medical Center between September 2012 and December 2017, with available records of intraoperative and postoperative test stimulation procedures, were retrospectively analyzed. The local Medical Ethics Committee waived formal evaluation of this study.

**Surgical procedure**

Surgery was performed with standard techniques (see supplementary material).[2, 9] Stereotactic frame-based 3D MRI was used for visually-adjusted targeting. Surgery was performed bilaterally, with patients awake, withdrawn from dopaminergic medication and sedatives. Two to four microelectrodes were inserted simultaneously ("Ben Gun"). Intraoperative stimulation was performed from the cannula tip. Permanent leads were implanted and centered along the best trajectory and depth, with the deepest contact not below the substantia nigra.

**Intraoperative stimulation**

Test stimulation with 60 µs and 130 Hz was performed with constant current at several depths with at least 2-mm distance along selected trajectories inside the STN. Mostly, 3 data-points per track were collected within the STN. Baseline symptom-severity was scored with the Unified Parkinson's Disease Rating Scale (UPDRS) items 20-22-23 prior to MER electrodes placement. Intensity was increased stepwise starting at 1 mA with 0.5 mA steps until debilitating side-effects appeared. Improvement of rigidity, tremor, and bradykinesia was recorded on standardized forms; only rigidity was used to reflect clinical improvement for purposes of accuracy and reliability. All persistent and debilitating side-effects were classified as either capsular (muscle twitching, dysarthria, gaze paresis) or non-capsular (diplopia, paresthesias, nausea, general discomfort), and dyskinesias. Other side-effects were transient (including paresthesias) or considered non-debilitating.



Aiming at maximum clinical benefit and enhancing comparability, the therapeutic window was defined as the difference between the required amplitude for obtaining maximal improvement of rigidity (UPDRS 0/1) and the threshold for inducing debilitating side-effects. When 'stun effects' relieved PD symptoms making scoring unreliable, or if no side-effects up to ≥4 mA, no therapeutic window was defined. If insufficient improvement, the therapeutic window was set at 0.

**Postoperative macrostimulation**

Postoperative monopolar contact review was performed by the same neurologist who performed the intraoperative examination, ±10 days after surgery when the device was switched on for the first time. Although unblinded, data from intraoperative stimulation was not used during the postoperative contact review. When directional leads were implanted, a standard omnidirectional monopolar contact review was performed at all levels. The procedure of the postoperative contact review was similar to the intraoperative test stimulation, except that conjugated eye movements were not systematically tested. The definitive contact for chronic stimulation was chosen based on the lowest threshold for optimal benefit or on the largest therapeutic window, at the physician's discretion.

**Outcome measures**

The postoperatively selected contacts and the contacts used at one-year follow-up were matched to corresponding intraoperative microstimulation depths, as previously described elsewhere.[2] In case of bipolar settings, the cathode was selected; in case of double monopolar settings, the middle was selected.

The best intraoperative depth was defined in two ways: the depth with the largest therapeutic

window, or with the lowest threshold for relieving rigidity. Additionally, all thresholds for clinical effects and therapeutic window sizes were compared between postoperatively selected contact points and stimulation at corresponding intraoperative depths, irrespective of whether these were the best intraoperative depths.

### Statistical analysis

Differences in symptom-severity, and therapeutic window sizes were compared using non-parametric Wilcoxon's signed rank tests. Symptom-severity was compared at each of the postoperatively selected contact points using non-parametric Kruskal-Wallis H-tests. To compare differences between intraoperative and postoperative thresholds, Gehan-Breslow-Wilcoxon survival analyses were performed. As chronic stimulation intensities commonly do not exceed 4.5 mA, results obtained at intensities >4,5mA were excluded. Analyses were performed using IBM SPSS 23 or GraphPad Prism 7.02.



## Results

A total of 145 PD patients underwent bilateral STN DBS in the selected period; 26 patients had missing records. We therefore included 119 consecutive patients (238 leads, 224 Medtronic 3389, 7 Vercise Cartesia) (table 4.1). For seven STNs, bipolar settings were chosen postoperatively; in all other STNs monopolar settings were used.

**Table 4.1.** Patient characteristics

| | |
|---|---|
| N | 119 |
| Age at surgery (years) | 60.5 (6.5) |
| Female sex (%) | 31.9 (n=38) |
| Preoperative UPDRS III rigidity score [a] | 2.8 (1.0) |
| Postoperative UPDRS III rigidity score [b] | 1.9 (1.3) |
| Preoperative UPDRS III bradykinesia score [a] | 2.7 (1.0) |
| Postoperative UPDRS III bradykinesia score [b] | 2.0 (1.2) |
| Preoperative UPDRS III tremor score [a] | 1.2 (1.3) |
| Postoperative UPDRS III tremor score [b] | 1.1 (1.3) |

Due to the limited range of the scores for symptom-severity, data is expressed as mean (standard deviation) for purposes of clarity.
[a] As scored during surgery, off medication, before starting of the procedure.
[b] As scored during the postoperative contact review, off medication.

### Postoperative stimulation site

The postoperatively selected contact was the most dorsal in 54 cases (23%), the second-most dorsal in 126 cases (54%), the second-most ventral in 46 cases (20%), and most ventral in seven cases (3%) (missing n=5).

In 34% of cases, the contact selected for chronic stimulation coincided with the intraoperative depth with the best therapeutic window and in 41% cases was immediately dorsal to it. In 38% of cases, the selected contact coincided with the intraoperative depth with the lowest threshold for rigidity improvement, and in 34% was immediately dorsal to it (figure 4.1).

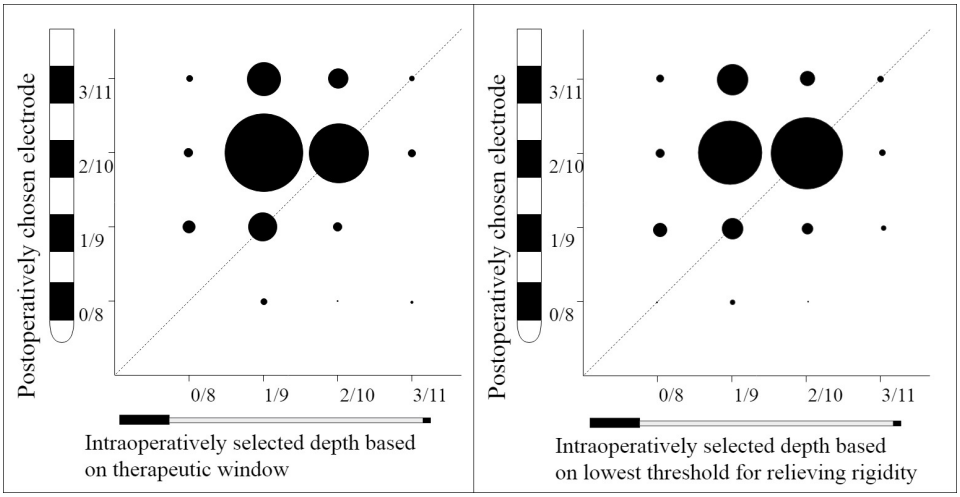


**Figure 4.1. Postoperative selected contact compared to intraoperatively selected depth.**
Depth selected for chronic stimulation, compared to the depth which intraoperatively yielded the largest therapeutic window (A), or the lowest threshold for rigidity (B). Dashed lines indicate perfect correlations. Circle-sizes reflect the number of sides.

After one-year follow-up, the contact point initially selected was maintained as monopolar, double monopolar or in bipolar configuration in 76% of leads (n=157/206).

There was no difference in the percentage of contacts that corresponded with the best intraoperative depth (or was immediately dorsal to it) at one year follow-up with respect to immediately after surgery.

**Induction of benefit and side-effects**

Intraoperatively (prior to MER insertion), UPDRS rigidity-scores were higher than during postoperative assessments ($Z=-7.47$, $p<0.001$, table 4.1), as were bradykinesia scores ($Z=-6.85$, $p<0.001$). Tremor was not different between assessments ($Z=-0.44$, $p=0.658$). There were no differences between the postoperatively selected contact points concerning baseline levels of rigidity ($X_2=3.57$, $p=0.312$), bradykinesia ($X_2=1.55$, $p=0.670$), or tremor ($X_2=0.60$, $p=0.898$).

A "stun effect" was observed intraoperatively in 4 sides and postoperatively in 22. There was no different trend for the finally chosen contact in these sides (middle two contact points selected in 75%).

During intraoperative stimulation, relief of rigidity (i.e. improvement to UPDRS 0/1) was observed in 97% of cases (n=186). For six sides debilitating side-effects occurred before rigidity relief. In 58% of cases, capsular side-effects were observed (n=125), non-capsular side-effects were observed in 13% of cases (n=27).

During postoperative stimulation, rigidity was relieved in 100% of cases (n=144). Capsular side-effects occurred in 60% of cases (n=117); non-capsular side-effects occurred in 16% (n=35). Intraoperatively, thresholds for relieving rigidity were lower than during postoperative stimulation at corresponding levels (intraoperative mean: 1.94 (0.80) mA vs. postoperative mean: 2.13 (0.83) mA, $X2=9.43$, $p=0.002$) (figure 4.2A), as were thresholds for inducing capsular side-effects (intraoperative mean: 3.15 (0.78) mA vs. postoperative mean: 3.34 (0.75) mA, $X2=5.69$, $p=0.017$) (figure 4.2B), whereas thresholds for inducing non-capsular side-effects were not different (intraoperative mean: 3.02 (0.96) mA vs. postoperative mean: 3.67 (0.91) mA, $X2=0.44$, $p=0.507$).



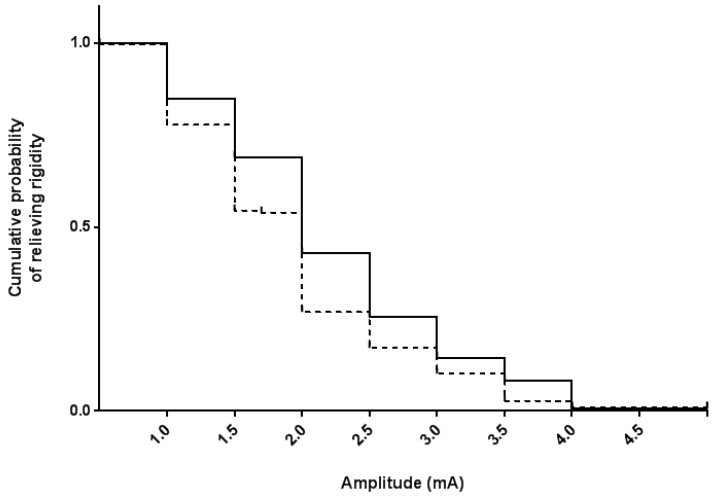


**Figure 4.2A. Intraoperative vs. postoperative stimulation intensity for relieving rigidity.**
Available intraoperative records: n=192, available postoperative records: n=144 (144 paired assessments. Dashed line: intraoperative assessment, continuous line: postoperative assessment. Vertical ticks indicates censoring. An event was characterized as relief of rigidity. When debilitating side-effects occurred at a certain threshold before rigidity was relieved, cases were censored at the threshold for side-effects (P=0.002).

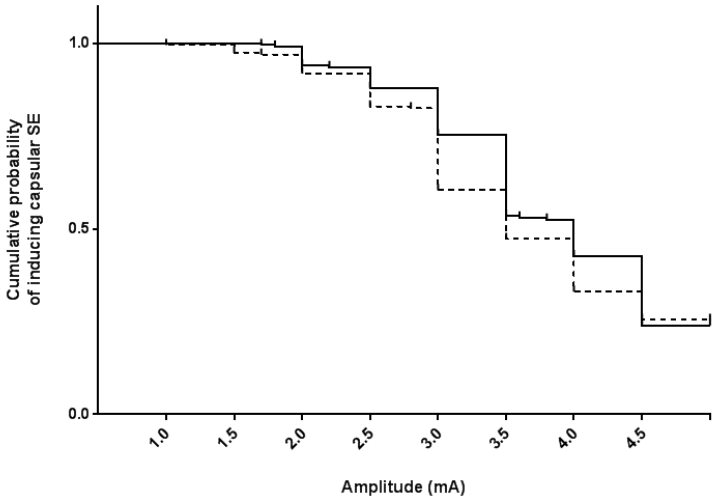


**Figure 4.2B. Intraoperative vs. postoperative stimulation intensity for inducing capsular side-effects.** Available intraoperative records: n=214, available postoperative records: n=195 (195 paired assessments. Dashed line: intraoperative assessment, continuous line: postoperative assessment. Vertical ticks indicates censoring. An event was characterized as occurrence of capsular side-effects (excluding gaze paresis). If no side-effects occurred, a case was censored at the highest tested level (p=0.016). SE = side-effect.

Widths of the therapeutic windows were not different between intra- and postoperative measurements (90 paired assessments, intraoperative mean: 1.36 (0.95) mA vs. postoperative mean: 1.42 (0.88) mA, Z=-0.20, p=0.844).

## Discussion

We investigated differences between intraoperative test stimulation and postoperative contact review. The majority of contacts selected for chronic stimulation corresponded to the intraoperative depth with the largest therapeutic window (or with the lowest threshold for relieving rigidity) or was immediately dorsal to it.

These results indicate that intraoperative testing can reduce the postoperative search space and improve efficiency by pointing to the two contacts with the highest chance of selection. This becomes even more important when directional leads (more stimulation options) are implanted. We recommend to initially focus on the two most promising contacts based on intraoperative testing, and test the other contacts only in case of unsatisfactory results. The selection of a more dorsal contact for chronic stimulation probably stems from the beneficial effects of stimulating the upper part of the STN, or the dorsally located zona incerta.[10-11]

The threshold for inducing non-capsular side-effects was not different between assessments, likely because of the small number of observations. However, both the thresholds for relieving rigidity and inducing capsular side-effects were lower intraoperatively than during the postoperative contact review. This should be considered during intraoperative decision-making. Various factors may have contributed to this, such as differences in 'volume of tissue activated' (VTA) between stimulation through electrodes with different designs, shape and position of the stimulating field, or differences in tissue impedance. At similar stimulation intensities, the VTA generated by MER electrodes is considerably larger than that generated by the definitive contact, which may partly explain our observations.[12] Furthermore, the macrostimulation tip [12-13] produces spherical VTAs [12] while the DBS electrodes produce a torus-shaped VTA [14] with an altered current vector, which may influence clinical effects (figure 4.3).[15, 16]



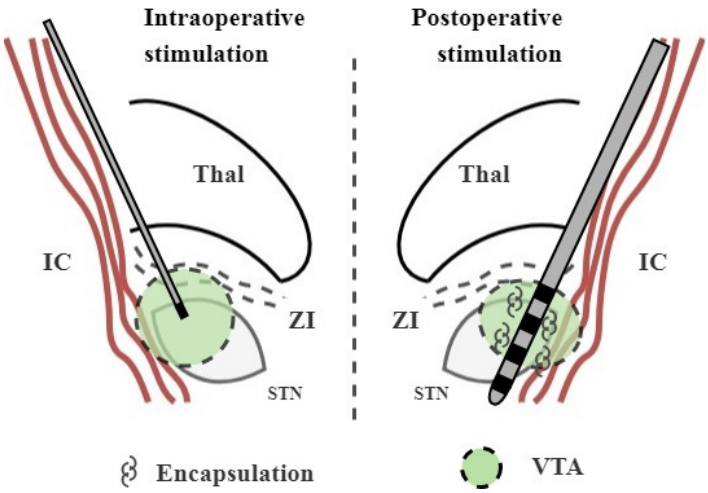


**Figure 4.3. Differences in electric fields between intraoperative and postoperative assessments.**
During intraoperative stimulation (left), the generated current is directed within a spherical VTA (green-shaded area), causing an outward current directionality that is similar in all directions.[12, 14] As the MER macrostimulation tip is newly introduced and relatively thin, there is no encapsulation yet. During the postoperative stimulation, the VTA is torus-shaped, resulting in a different current vector which is more perpendicular to the IC anisotropy, causing lower degree of activation.[15, 16] As a result of the increased encapsulation, the impedance surrounding the DBS lead is increased [25-27] which causes a different propagation of the electric current around the DBS lead, as well as a smaller VTA [12] with less current spreading over the STN, ZI and IC.
This figure is solely for schematic purposes; the drawn structures may not reflect the actual anatomic proportions.
IC: internal capsule; STN: subthalamic nucleus, Thal: thalamus; VTA: volume of tissue activated; ZI: zona incerta.

The lower baseline levels of rigidity during postoperative testing may partly be explained by persistent stun effects, generated after definitive lead insertion.[17-18] Even though stun effects

are predictive of the ultimate effectiveness of DBS,[19] they might impair or even preclude optimization of DBS settings at early stages.[20] Performing the postoperative review later might result in less stun effects. Moreover, our patients underwent complete dopaminergic medication withdrawal before surgery, and only an overnight medication withdrawal before postoperative contact review; carryover effects of medication cannot be excluded. However, whereas this could explain differences in thresholds for relieving rigidity, it does not explain differences in inducing side-effects.

Our observation of lower intraoperative than postoperative thresholds for relieving rigidity is supported by previous literature,[2] although the threshold for side-effects in that study was lower during postoperative stimulation, which lead to significant differences in the therapeutic windows as opposed to our findings. A possible reason for this discrepancy is that this study performed the postoperative stimulation using a constant-voltage mode, whereas intraoperative stimulation was performed with constant current mode.[21, 22]



A study investigating 12 dystonia patients (GPi DBS) found a small trend towards lower postoperative thresholds for capsular side-effects,[23] which increased after 6-17 months. Intraoperative evaluation was performed under general anesthesia, which might account for increased thresholds for capsular side-effects. Moreover, thresholds of self-reported side-effects or dysarthria cannot be recorded under anesthesia.[24]

Strengths of this study include the large sample size, standardized procedures, and standardized reporting of clinical effects. Possible limitations include the retrospective design and inherent missing data. Although the assessment order differed (intraoperatively dorsal-to-ventral; postoperatively ventral-to-dorsal), a carryover effect was likely limited due to sufficient waiting time and return to baseline symptom-levels.

Future studies may apply prospective designs to minimize missing data. Additionally, replication of these results in other targets may confirm whether they are specific for the STN and surrounding anatomical structures.

To what extent these results may ultimately aid in improving the efficiency of postoperative contact review remains to be explored.

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## Supplementary material

For target localization, stereotactic frame-based 3D magnetic resonance imaging (MRI) and StealthStation™ planning software (Medtronic, Minneapolis, Minnesota, USA) were used. The STN was generally localized at 12 mm lateral, 2 mm posterior and 4 mm inferior to the midcommissural point; individual adjustments were made after visual inspection of T2-weighted MRI scans. Path planning started just in front of the coronal suture and with 20-30° lateral angulation to the midline, with individual adjustments made to avoid blood vessels, sulci, and ventricles. Lead-implantation was performed with patients awake, withdrawn from dopaminergic medication and sedatives. Dopamine agonists were gradually reduced and stopped at least 3 days prior to surgery; levodopa was stopped at least 24 hours prior to surgery. Procedures were performed bilaterally. MERs were obtained by inserting 2 to 4 parallel cannulas and microelectrodes simultaneously (FHC, Bowdoin, Maine, USA) in a 2 mm interspace "Ben Gun" array. Intraoperative stimulation was performed using the microelectrode stimulation tip (semi-microstimulation). The permanent leads (model 3389, Medtronic, Minneapolis, Minnesota, USA; or model Vercise Cartesia™, Boston Scientific, Marlborough, Massachusetts, USA) were subsequently implanted along the best trajectory. After MER and intraoperative test stimulation, permanent leads were usually positioned with the middle two contacts placed at the level with best stimulation effect, provided that the deepest contact was not below the substantia nigra. The pulse generator was placed under general anesthesia during the same surgical session and connected to the permanent leads.